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### Accepted Article

**Title:** Highly Enantioselective, Organocatalytic and Scalable Synthesis of a rare cis-cis-Tricyclic Diterpenoid

**Authors:** Alexander John Andre Cobb, Daniel Townsend, Kenneth Shankland, Alex Weymouth-Wilson, Zofia Komsta, and Tim Evans

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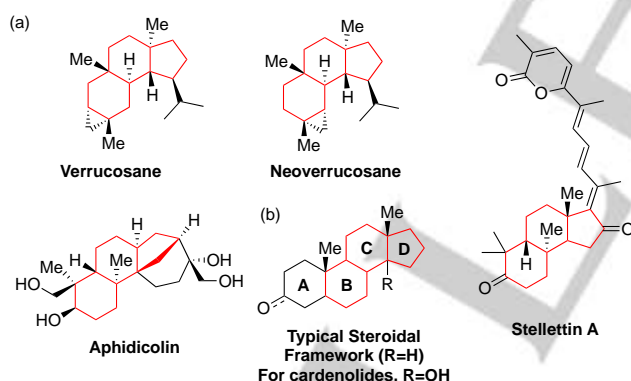
## COMMUNICATION

# Highly Enantioselective, Organocatalytic and Scalable Synthesis of a rare *cis-cis*-Tricyclic Diterpenoid

Daniel Townsend,<sup>[a]</sup> Kenneth Shankland,<sup>[b]</sup> Alex Weymouth-Wilson,<sup>[c]</sup> Zofia Komsta,<sup>[c]</sup> Tim Evans,<sup>[c]</sup> and Alexander J. A. Cobb\*<sup>[a]</sup>

**Abstract:** A highly enantioselective, organocatalytic and scalable synthesis of a very unusual *cis*-decalin-*cis*-hydrindane tricyclic diterpenoid system has been achieved. Despite the prevalent pharmacological space that the related *trans-trans* and *trans-cis*-systems occupy, there have been no reports of an asymmetric synthesis of the *cis-cis* systems in the literature until now. We demonstrate the flexibility of our approach not only through access to a diverse range of products, all of which are attained in exceptionally high selectivities, but also by showing their easy conversion to the corresponding *trans-cis*-system and other derivatives.

Diterpenes and triterpenes such as steroids are amongst the most important and well-studied class of biomolecule owing to their incredibly broad biological properties, their fascinating chemistry, and their spectrum of therapeutic potential.<sup>[1]</sup> Although tricyclic systems whereby there exists a decalin unit fused to a hydrindane one only occur in a handful of diterpenes discovered thus far – e.g. verrucosane,<sup>[2]</sup> neoverrucosane<sup>[3]</sup> and the stellettins (Figure 1a),<sup>[4]</sup> this tricyclic arrangement is ubiquitous within almost every steroidal system known. Referred to as the BCD ring system, these three rings are the source of most of the structural diversity within steroidal systems (Figure 1b). It is no surprise, therefore, that the expedient synthesis of these scaffolds has been the focus of much study over the last half century.<sup>[5]</sup>



**Figure 1:** Example natural product frameworks where a decalin is fused to a hydrindane

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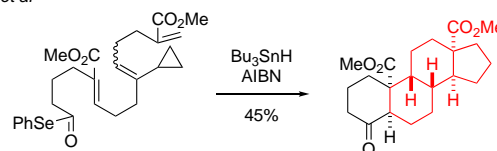
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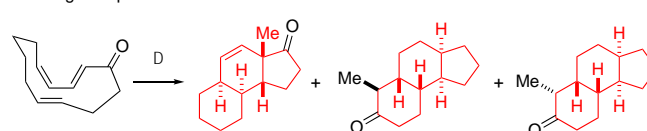
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Nevertheless, although in synthetic terms the *trans*-decalin-*trans*-hydrindanes and to a lesser extent the *trans*-decalin-*cis*-hydrindane systems (as occur in the cardenolides) are well established, other stereochemical variations are extremely rare. This is astonishing given that alternative unnatural configurations offer the potential to explore new pharmacological space. Specifically, examples of a *cis*-decalin fused to a *cis*-hydrindane are extremely rare; either in steroidal syntheses or otherwise.<sup>[6]</sup> In fact, we could find just three examples of this framework in the literature, none of which were enantioselective or capable of achieving any significant structural diversity. Pattenden and co-workers serendipitously accessed the steroidal target containing this fragment *via* a radical cascade reaction (Figure 2a).<sup>[6a]</sup> The second example by Deslongchamps and co-workers led to three different isomers of these systems *via* a transannular Diels-Alder reaction (Figure 2b).<sup>[6b]</sup> Finally, Kocór and co-workers demonstrated a dynamic kinetic resolution a cardenolide-like precursor to give the corresponding *cis*-decalin-*cis*-hydrindane (Figure 2c).<sup>[6c]</sup> Our approach to constructing this system was to use organocatalytic methodology – specifically using the nitro group as a handle – a functionality we have exploited with some success in the past.<sup>[7]</sup> In addition, we felt that not only would this unique *cis-cis* tricyclic structure enable the exploration of undiscovered chemical space, but would also be dynamic enough as a central fragment to derivatize easily to other terpenoid structures, owing to the orthogonal reactivity of the functional group handles on each ring system.

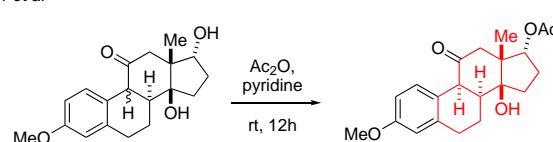
Pattenden *et al*<sup>6a</sup>



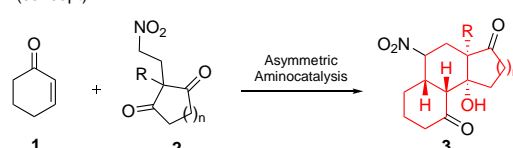
Deslongchamps *et al*<sup>6b</sup>



Kocór *et al*<sup>6c</sup>



This work (concept)



**Figure 2:** None of the three literature examples of *cis*-decalin-*cis*-hydrindane tricyclic syntheses are enantioselective, nor open to significant substrate scope.

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In our design we sought to use asymmetric aminocatalysis to encourage an enantioselective Michael addition of nitrocyclopentadione **2** to cyclohexanone **1**. We hoped that the resulting enolate would undergo an intramolecular desymmetrising aldol reaction with the resulting dione to form the desired tricyclic system. The latter part of this sequence is of course known, originating from the works of Hajos-Parrish<sup>[8]</sup> and Eder, Sauer and Wiechert.<sup>[9]</sup> More recently, the excellent work of both Nagorny<sup>[10]</sup> and Deslongchamps<sup>[11]</sup> constructed the *cis*-hydrindane, fused to a *trans*-decalin in a variety of cardenolides through such a desymmetrising process, giving us hope that this approach would be valid for our target.

To test the feasibility of our hypothesis, our investigation began by screening the reaction of **1** and **2** with a range of catalytic systems, each of which have been utilized to varying degrees of success in conjugate addition chemistry, along with 3-nitrobenzoic acid as a co-catalyst additive (Table 1). Surprisingly, neither the Hayashi-Jørgensen<sup>[12]</sup> **I**, nor the MacMillan<sup>[13]</sup> **II** systems catalyzed the process to any degree (Entries 1 and 2). Bifunctional thiourea systems **III** were also unsuccessful (Entry 3).<sup>[14]</sup> To our delight, however, proline **IV**, proline tetrazole<sup>[15]</sup> **V** and the primary amine cinchona alkaloid<sup>[16]</sup> **VI** gave us the product we desired (Entries 4-6).

Whilst the proline catalysts only directed the reaction with moderate selectivity, we were very pleased to see that the well-established conjugate addition catalyst **VI** was able to control the

reaction with exceptional stereocontrol. Interestingly, for all catalysts **IV** to **VI**, the tricyclic product was produced as a single diastereoisomer, whilst the acyclic intermediate **4**, representing the majority of the product, was obtained in a 1:1 dr, suggesting epimerization under the reaction conditions. In the case of catalyst **VI**, these diastereoisomers were produced as *single* enantiomers.

The absolute stereochemistry of tricyclic system **3**, showing the *cis-cis* arrangement of the system (Figure 3) was established by reference to tricyclic system **6** (Figure 6), whose absolute stereochemistry was determined unambiguously by X-ray crystallography.



**Figure 3** : One of the two unique molecules in the asymmetric unit of the crystal structure of tricyclic adduct **3a**. The other molecule differs only in terms of the rotation of the nitro group (CCDC : 1967524)

Our attention then focused on improving the yield of the reaction. Although the organocatalyst was unable to push the reaction all the way to the tricycle, we theorized that if we could optimize the formation of acyclic intermediate product **4**, which was the major product anyway, we could then force the subsequent cyclization using alternative conditions (Table 2). It was found that the co-catalyst used was critical to the success of the reaction, and that changing the solvent also had a profound effect on yield. The

**Table 1.** Organocatalyst screen for the Michael-Aldol sequence between cyclohexanone **1** and nitroalkane **2**.<sup>[a]</sup>

Entry	Catalyst	Yield <b>3a</b> (%)	ee <b>3a</b> (%)	Yield <b>4a</b> (%) <sup>[b]</sup>	ee <b>4a</b> (%) <sup>[c]</sup>
1	<b>I</b>	0	-	0	-
2	<b>II</b>	0	-	0	-
3	<b>III</b>	0	-	0	-
4	<b>IV</b>	8	-52	16	nd
5	<b>V</b>	12	-42	18	nd
6	<b>VI</b>	12	>99	58	>99, >99

[a] Reactions performed on a 1 mmol scale [b] Isolated as a mixture of diastereoisomers [c] Determined by chiral HPLC analysis

**Table 2.** Solvent screen for the Michael addition between cyclohexanone **1** and nitroalkane **2**.<sup>[a]</sup>

Entry	Solvent	1 : 2	Co-catalyst	T, °C	time, h	Yield <b>4a</b> (%) <sup>[b]</sup>	ee <b>4a</b> (%) <sup>[c]</sup>
1	CH <sub>2</sub> Cl <sub>2</sub>	1 : 1	2-FBA	23	168	0	-
2	CH <sub>2</sub> Cl <sub>2</sub>	1 : 1	AcOH	23	168	0	-
3	CH <sub>2</sub> Cl <sub>2</sub>	1 : 1	p-TSA	23	168	0	-
4	MeCN	1 : 1	3-NBA	23	96	32	92, 96
5	PhMe	1 : 1	3-NBA	23	24	41	95, 98
6	CHCl <sub>3</sub>	1 : 1	3-NBA	23	72	59	97, 98
7	THF	1 : 1	3-NBA	23	72	48	>99, >99
8	MeOH	1 : 1	3-NBA	23	24	43	86, 91
9	CH <sub>2</sub> Cl <sub>2</sub>	1 : 1	3-NBA	40	24	55	96, 96
10	CH <sub>2</sub> Cl <sub>2</sub>	2 : 3	3-NBA	23	48	59	>99, >99
11	CH <sub>2</sub> Cl <sub>2</sub>	2 : 1	3-NBA	23	48	70	>99, >99

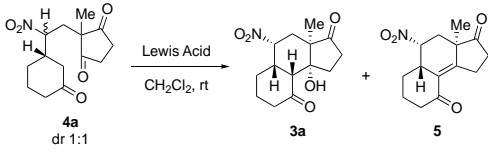
[a] Reactions performed on a 1 mmol scale [b] Isolated as a 1:1 mixture of diastereoisomers as determined by <sup>1</sup>H NMR [c] Determined by chiral HPLC analysis.

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most significant effect on selectivity, however, came from the stoichiometry of the process, with two equivalents of cyclohexene giving Michael adduct **4** in exceptional enantioselectivity.

With an excellent synthesis of tricyclic precursor **4** in hand, we then went on to examine conditions to enable the cyclization. Whilst both Brønsted acid and base conditions led to substrate degradation, primarily through a retro-Michael pathway,<sup>[17]</sup> we were delighted to discover that a screen of Lewis Acids resulted in the formation of the desired adduct, observed previously (Table 3). The initial catalyst screen resulted in the observation of elimination product **5**, but a screen of solvent, temperature and stoichiometry led to us finding the optimal conditions for the exclusive formation of the *cis*-decalin-*cis*-hydrindane **3a** in good yield.

**Table 3.** Lewis acid screen for the Aldol cyclization of **4a**.<sup>[a]</sup>



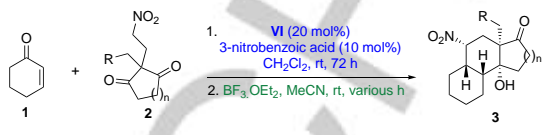
Entry	Lewis Acid (eqs)	Solvent	T, h	Yield <b>3</b> , %	Yield <b>5</b> , %
1	SnCl <sub>4</sub> (1.2)	CH <sub>2</sub> Cl <sub>2</sub>	72	0	0
2	BF <sub>3</sub> ·OEt <sub>2</sub> (1.2)	CH <sub>2</sub> Cl <sub>2</sub>	24	33	17
3	TiCl <sub>4</sub> (1.2)	CH <sub>2</sub> Cl <sub>2</sub>	72	0	0
4	AlCl <sub>3</sub> (1.2)	CH <sub>2</sub> Cl <sub>2</sub>	72	8	6
5	BF <sub>3</sub> ·OEt <sub>2</sub> (1.2)	PhMe	96	17	25
6	BF <sub>3</sub> ·OEt <sub>2</sub> (1.2)	MeCN	96	53	4
7	<b>BF<sub>3</sub>·OEt<sub>2</sub> (2)</b>	<b>MeCN</b>	<b>5</b>	<b>79</b>	<b>0</b>
8	BF <sub>3</sub> ·OEt <sub>2</sub> (3)	MeCN	5	73	0

[a] Reactions performed on a 0.7 mmol scale.

With our optimized conditions in hand, we examined the generality of this process using a range of different substrates as shown in Table 4. We were very pleased to observe that the selectivities were excellent for all substrates, showing only a single diastereoisomer and >99% enantiomeric excess for most. Remarkably, there appear to be no general methodologies to allow for variation in the substituent at the hydrindane bridgehead position of any terpene or steroidal target. Indeed, the only departure from methyl at that position appear to be the progesterone oral contraceptives, which have ethyl or hydroxymethyl variations at that position. Our methodology addresses this paucity and thus opens the door to greater pharmacological space. We have successfully introduced larger substituents such as isopropyl (**3b**) and 1-naphthyl (**3h**) in good yield and excellent selectivity, as well as thiophene (**3g**), benzyl (**3e**) and para-chlorobenzyl (**3i**) which are all capable of further derivation. Pleasingly, we also used our methodology to successfully access the D-homosteroid-like system (**3j**) – again in excellent diastereo- and enantioselectivity.<sup>[21]</sup> Use of

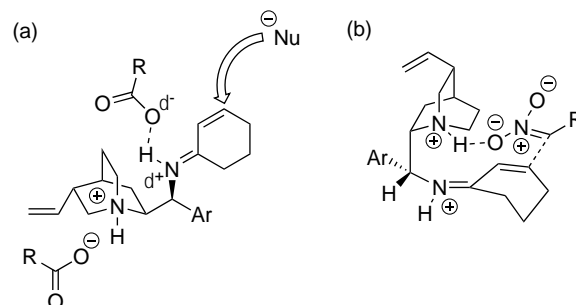
cycloheptene in place of partner **1** gave the single addition product **4k** – again in 1:1 dr and excellent enantioselectivities for both diastereoisomers – but unfortunately did not cyclize to the tricyclic system under our current conditions.

**Table 4.** Substrate scope for the synthesis of *cis*-*cis*-tricyclic systems.<sup>[a]</sup>



<b>3a</b>	70% 80%, 5 h >19:1 dr >99% ee
<b>3b</b>	73% 60%, 45 h >19:1 dr 98% ee
<b>3c</b>	74% 73%, 16 h >19:1 dr 98% ee
<b>3d</b>	72% 65%, 7 h >19:1 dr >99% ee
<b>3e</b>	82% 61%, 16 h >19:1 dr >99% ee
<b>3f</b>	75% 57%, 16 h >19:1 dr 98% ee
<b>3g</b>	71% 44%, 16 h >19:1 dr >99% ee
<b>3h</b>	75% 62%, 16 h >19:1 dr >99% ee
<b>3i</b>	69% 59%, 16 h >19:1 dr >99% ee
<b>3j</b>	81% 65%, 60 h >19:1 dr >99% ee
<b>4k</b>	41% 1:1 dr 99% ee (both)

[a] Reactions scales vary depending on substrate, see SI for details. Ee determined by chiral HPLC analysis.



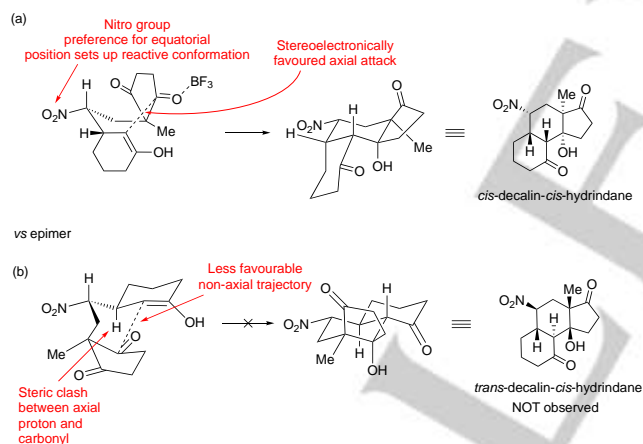
**Figure 4 :** Although the stereoselective outcome of our process fits the model of Melchiorre (Figure 4a, ref 17), our stoichiometry and co-catalyst are slightly different. (b) Bifunctional activation of the enone and nucleophile is also a possibility (ref 16).

Although the origin of stereochemistry in the Michael addition fits the model proposed by Melchiorre and co-workers (Figure 4a),<sup>[17]</sup> which describes optimal conditions of 2:1 co-catalyst to



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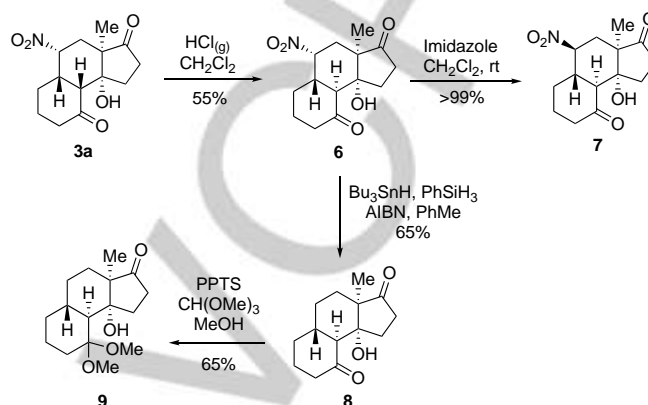
amine catalyst, we found that better yields were obtained in a 1:2 ratio (Table 1, Entry 11). We therefore do not discount the possibility of a bifunctional effect of the catalyst on the enantioselective outcome (Figure 4b), as has been described for other related processes,<sup>[16]</sup> although further study is required. Under the reaction conditions, the  $\alpha$ -proton of the nitro group epimerizes, giving a 1:1 mix of diastereoisomers as is evident in Table 2. This epimerization also occurs under the subsequent Lewis acid conditions, which is a critical point because we theorize that only *one* of these epimers is able to cyclize under these conditions. This is demonstrated in Figure 5, where both epimers are shown in the conformations they are required to adopt in order to cyclize. Our main assumption is that in both, the large nitro group must adopt an equatorial-like position in the transition state. For the preferred (*R*)-epimer (Figure 5a), this sets up the stereoelectronic requirements for favourable axial attack. As one might expect, this also sets up the preference for the reacting group to approach from the face on which it resides, giving the observed *cis*-geometry. In the case of the (*S*)-epimer, the nitro group is again assumed to prefer an equatorial-like position (Figure 5b), but this time in order for the corresponding nitronate to react, it needs to come in from the *anti*-face. This is very unfavorable owing to the resulting steric demands where there is a steric clash between the  $\beta$ -hydrogen and the reacting carbonyl. Thus, as the substrate epimerizes, and more of the favored epimer is generated, the reaction is driven towards the cyclized product.



**Figure 5** : The requirement for the nitro-functionality to reside in a pseudo-equatorial position means that only one of the two epimers is set up to cyclize. Since the starting material epimerizes under the reaction conditions, this means that the overall reaction is driven toward the formation of the preferred epimer and thus the cyclized product. (a) The reactive epimer leads to the *cis*-*cis*-tricyclic. (b) The other epimer does not have the steric or stereoelectronic requirements to cyclize.

In order to demonstrate that it was also possible to access the more common *trans*-decalin-*cis*-hydrindane from these systems, we subjected tricyclic system **3a** to HCl gas in dichloromethane and pleasingly obtained the corresponding C-10 epimer **6** (Scheme 1). Interestingly, this leads to the nitro-group going from an equatorial position to an axial one (Figure 6), which is demonstrated by the fact that treatment of compound **6** with

imidazole leads to C-6 epimer **7** where the nitro group is now in a preferred, thermodynamically favourable equatorial position. Finally, we have also demonstrated that the nitro-group can be removed altogether *via* a radical denitration to obtain tricycle **8**, and that it is possible to discriminate between the two ketones of the product by selective acetal protection of the cyclohexanone.



**Scheme 1.** Epimerization of tricycle **3a** and subsequent transformations.



**Figure 6** : X-Ray crystal structure of the epimerized *trans*-decalin-*cis*-hydrindane system **6**, showing that the nitro group is now axial (CCDC: 1967525)

In conclusion, we have developed the first enantioselective synthesis of a *cis*-decalin-*cis*-hydrindane tricycle. Adducts were obtained in exceptionally good selectivities and a model rationalizing this is proposed. It was also shown that we could access a diverse range of structural configurations, such as the C9-C10 unsaturated system **5** and the C10-epimer **6**. We also showed it was possible to epimerize the nitro group effectively, as well as remove it altogether. Future work will focus on examining the biological activity of these systems and their derivatives as well as utilizing them towards the synthesis of cardenolide analogues.

## Acknowledgements

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## COMMUNICATION

**Keywords:** terpenes • asymmetric synthesis • organocatalysis •  
• *cis*-hydrindane • *cis*-decalin

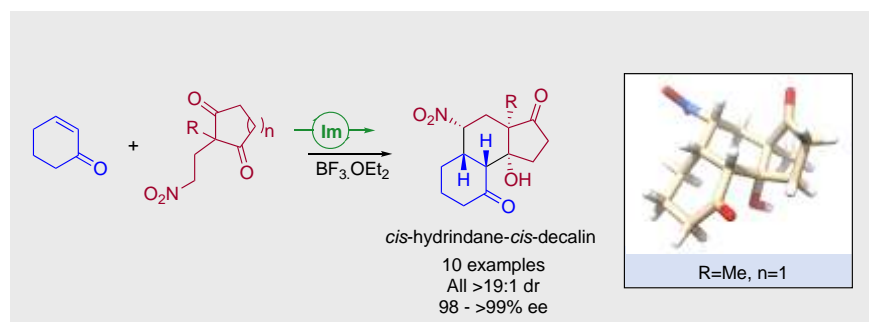
- [1] a) *Terpenes: Flavors, Fragrances, Pharmaca, Pheromones* (Ed.: E. Breitmaier), Wiley-VCH, Weinheim, **2006**. b) Daniel Lednicer in *Steroid Chemistry at a Glance*, John Wiley & Sons, **2010**.
- [2] D. Takaoka, A. Matsuo, M. Nakayama, S. Hayashi, *Phytochemistry* **1983**, *22*, 1653-1655.
- [3] a) T. Hashimoto, I. Nakamura, M. Tori, S. Takaoka, Y. Asakawa, *Phytochemistry* **1995**, *38*, 119-127. b) A. Spyere, D. C. Rowley, P. R. Jensen, W. Fenical, *J. Nat. Prod.* **2003**, *66*, 818-822.
- [4] J. Y. Su, Y. H. Meng, L. M. Zeng, X. Fu, F. J. Schmitz, *J. Nat. Prod.* **1994**, *57*, 1450-1451
- [5] e.g. a) D. Urabe, T. Asaba, M. Inoue, *Chem. Rev.* **2015**, *115*, 9207-9231; b) Y. Chen, J. Zhao, S. Li, J. Xu, *Nat. Prod. Rep.* **2019**, *36*, 263-288; c) M. Kitora, F. Hessler, B. Eignerová, *Eur. J. Org. Chem.* **2012**, 29-42; d) P. Gupta, G. Panda, *Eur. J. Org. Chem.* **2014**, 8004-8019; e) Z. G. Brill, M. L. Condakes, C. P. Ting, T. J. Maimone, *Chem. Rev.* **2017**, *117*, 11753-11795.
- [6] a) S. Handa, G. Pattenden, *Chem. Commun.* **1998**, 311-312; b) K. Baettig, C. Dallaire, R. Pitteloud, P. Deslongchamps, *Tetrahedron Lett.* **1987**, *28*, 5249-5252; c) A. R. Daniewski, M. Guzewska, M. Kocór *J. Org. Chem.* **1978**, *43*, 349-350.
- [7] a) L. S. Aitken, N. R. Arezki, A. Dell'Isola, A. J. A. Cobb, *Synthesis* **2013**, *45*, 2627-2648; b) W. Al-Ani, K. Shankland, A. J. A. Cobb *Synlett* **2016**, *27*, 17-20; c) S. Rajkumar, K. Shankland, G. D. Brown, A. J. A. Cobb, *Chem. Sci.* **2012**, *3*, 584-588; d) W. J. Nodes, K. Shankland, S. Rajkumar, A. J. A. Cobb, *Synlett* **2010**, 3011-3014; e) W. J. Nodes, D. R. Nutt, A. M. Chippindale, A. J. A. Cobb, *J. Am. Chem. Soc.* **2009**, *131*, 16016-16017. f) R. Fanelli, D. Berta, T. Földes, R. A. Atkinson, H.-J. Hofmann, K. Shankland, A. J. A. Cobb, *J. Am. Chem. Soc.* DOI: 10.1021/jacs.9b10861
- [8] a) Z. G. Hajos, D. R. Parrish, German Patent DE 2102623 **1971**; b) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615-1621
- [9] U. Eder, G. Sauer, R. Wiechert, *Angew. Chem. Int. Ed.* **1971**, *10*, 496-497.
- [10] a) H. R. Khatri, B. Bhattarai, W. Kaplan, Z. Li, M. J. C. Long, Y. Aye, P. Nagorny, *J. Am. Chem. Soc.* **2019**, *141*, 4849-4860; b) B. Bhattarai, P. Nagorny, *Org. Lett.* **2018**, *20*, 154-157; c) W. Kaplan, H. R. Khatri, P. Nagorny, *J. Am. Chem. Soc.* **2016**, *138*, 7194-7198; d) N. R. Cichowicz, W. Kaplan, Y. Khomutnyk, B. Bhattarai, Z. Sun, P. Nagorny, *J. Am. Chem. Soc.* **2015**, *137*, 14341-14348.
- [11] M. S. Reddy, H. Zhang, S. Phoenix, P. Deslongchamps *Chem. Asian J.* **2009**, *4*, 725-741.
- [12] a) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 794-797; b) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *44*, 4212-4215; c) J. Franzen, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjarsgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296-18304.
- [13] a) W. S. Jen, J. J. M. Wiener, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 9874-9875; b) N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2001**, *123*, 4370-4371; c) M. P. Brochu, S. P. Brown, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2004**, *126*, 4108-4109; d) T. D. Beeson, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 8826-8828.
- [14] a) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119-125; b) B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967-1969; c) S. H. McCooey, S. J. Connon, *Angew. Chem. Int. Ed.* **2005**, *44*, 6367-6370; d) J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481-4483.
- [15] a) A. J. A. Cobb, D. M. Shaw, S. V. Ley, *Synlett* **2004**, 558-560; b) A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem.* **2005**, *3*, 84-96; c) H. Torii, M. Nakadaï, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem., Int. Ed.* **2004**, *43*, 1983-1986; d) A. Hartikka, P. I. Arvidsson, *Tetrahedron: Asymmetry* **2004**, *15*, 1831-1834; e) A. Hartikka, P. I. Arvidsson, *Eur. J. Org. Chem.* **2005**, 4287-4295.
- [16] For excellent reviews, see: a) P. Melchiorre, *Angew. Chem. Int. Ed.* **2012**, *51*, 9748-9770; b) J. Duan, P. Li, *Catal. Sci. Technol.* **2014**, *4*, 311-320; c) L.-Y. Wu, G. Bencivenni, M. Mancinelli, G. Bartoli, P. Melchiorre, *Angew. Chem. Int. Ed.* **2009**, *48*, 7196-7199; d) L.-W. Xu, J. Luo, Y. Lu, *Chem. Commun.* **2009**, 1807-1821.
- [17] A. Moran, A. Hamilton, C. Bo, P. Melchiorre, *J. Am. Chem. Soc.* **2013**, *135*, 9091-9098.

## COMMUNICATION

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## COMMUNICATION



Daniel Townsend, Kenneth Shankland,  
Alex Weymouth-Wilson, Zofia Komsta,  
Tim Evans, and Alexander J. A. Cobb\*

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**Highly Enantioselective,  
Organocatalytic and Scalable  
Synthesis of a rare *cis-cis*-Tricyclic  
Diterpenoid**

The highly enantioselective synthesis of a tricyclic terpenoid system is described with a remarkable *cis-cis*-configuration of the fused decalin and hydrindane systems. This intriguing selectivity is thought to be due to the nitro-group dictating the transition state of the cyclization adopted.